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EFFECT OF COPPER(II) TRIFLATE ON INTRAMOLECULAR DIELS–ALDER REACTION OF OXAZOLE–OLEFINS

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Abstract - Intramolecular Diels–Alder reaction of the oxazole–olefins (**8a**) and (**11a**) was effectively promoted by addition of a catalytic amount of copper(II) triflate to afford the cyclopenta[*c*]pyridines (**9a**) and (**12a**), respectively.

Oxazoles have been known to participate as azadiene components in Diels–Alder reactions with olefinic dienophiles to give pyridine derivatives.¹ Since an intramolecular version of this cycloaddition was reported for the first time by Levin and Weinreb,² it has been occasionally used for the synthesis of annulated pyridines.³ Although we have recently achieved the synthesis of two monoterpene alkaloids, (–)-plectrodorine (**3a**) and (+)-oxerine (**3b**), possessing a cyclopenta[*c*]pyridine ring system, the yields of the intramolecular Diels–Alder reaction of the oxazole–olefins (**1a,b**) exploited as a key step of the synthesis were significantly low (**2a**; 37%, **2b**; 23%).⁴ This led us to investigate the effect of Lewis acids on the corresponding cycloaddition of the dimethyl substituted derivatives (**8a**) and (**11a**) and the unsubstituted congeners (**8b**) and (**11b**), selected as models for **1a** and **1b**.

The requisite oxazole–olefins (**8a,b**) and (**11a,b**) were prepared from the lactones (**4a,b**) according to our previous procedure for **1a,b**.⁴ Thus, treatment of α,α -dimethyl- γ -butyrolactone (**4a**)⁵ with 2.5 equiv. of α -lithiated methyl isocyanide⁶ in THF at -78°C for 3 h, followed by quenching with AcOH provided the oxazole alcohol (**5a**) in 85% yield. After Swern oxidation⁷ of **5a** to the oxazole aldehyde (**6a**) in 93% yield, Grignard reaction with vinylmagnesium bromide was performed in THF at -10°C , furnishing the allylic alcohol (**7a**) in 90% yield. The desired **8a** was then readily obtained from **7a** in 85% yield by oxidation with the Dess–Martin periodinane.⁸ On the other hand, coupling reaction of **6a** with methyl *trans*-3-iodoacrylate⁹ was carried out in DMSO by using CrCl₂ and a catalytic amount of NiCl₂ according to

Kishi's modification¹⁰ of the Nozaki conditions¹¹ to afford **10a** (59% yield), which was also converted into **11a** in 86% yield by a similar oxidation. A parallel sequence of reactions starting from γ -butyrolactone (**4b**) and proceeding through the intermediates (**5b**; 89%), (**6b**; 67%), (**7b**; 85%), and (**10b**; 52%) provided the unsubstituted substrates (**8b**; 84%) and (**11b**; 71%).

With four model oxazole-olefins (**8a,b**) and (**11a,b**) in hand, we first examined the intramolecular Diels-Alder reaction of **8a** in detail. As listed in Table I, heating a 0.05 M solution of **8a** in *o*-dichlorobenzene (*o*-DCB) at 150°C under argon for 24 h provided the cyclopenta[*c*]pyridine (**9a**); the yield, however, was only 21% (Entry 2). Although Weinreb *et al.* used DBN successfully in intramolecular oxazole-olefin Diels-Alder reactions,^{2,3b} no formation of **9a** was observed in the presence of the amidine (Entry 3). As the first example of Lewis acid catalysis in oxazole-olefin cycloadditions, Levin recorded the results of investigation on the effect of a europium salt.^{3c} In the case of **8a**, however, addition of $\text{Eu}(\text{fod})_3$ failed to improve the yield of **9a** (Entry 4). Fortunately, several metal triflates, such as $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, and $\text{Cu}(\text{OTf})_2$, proved to be effective to carry out the cycloaddition of **8a** (Entries 5–7). The best result was obtained by heating **8a** in *o*-DCB in the presence of 2 mol % of $\text{Cu}(\text{OTf})_2$ at 180°C for 1 h; under these conditions, **9a** was produced in 55% yield (Entry 9).

Dramatic rate enhancement was observed for the cycloaddition of **11a** possessing an ester group on the terminal olefin when a catalytic amount of $\text{Cu}(\text{OTf})_2$ was employed (Table II). In the absence of the catalyst, **12a** was obtained in only 15% yield together with unaltered **11a** (73%) after 24 h at 150°C (Entry 4), whereas smooth cycloaddition occurred in the presence of 2 mol % of $\text{Cu}(\text{OTf})_2$, giving **12a** in 95% yield after 30 min (Entry 6). Addition of $\text{Eu}(\text{fod})_3$ again failed to effect any improvement (Entry 5). Under

the influence of 10 mol % of $\text{Cu}(\text{OTf})_2$, the above reaction proceeded even at a lower temperature (Entries 1 and 3).

TABLE I. Intramolecular Diels–Alder Reactions of **8a**

Entry	Solvent	Additive (mol %)	Temp., °C	Time, h	Yield (%) of 9a
1	Toluene	$\text{Cu}(\text{OTf})_2$ (10)	Reflux	24	26
2	<i>o</i> -DCB	—	150	24	21
3	<i>o</i> -DCB	DBN (75)	150	2	0
4	<i>o</i> -DCB	$\text{Eu}(\text{fod})_3$ (10)	150	8	8
5	<i>o</i> -DCB	$\text{Yb}(\text{OTf})_3$ (10)	150	2	37
6	<i>o</i> -DCB	$\text{Sc}(\text{OTf})_3$ (10)	150	3	40
7	<i>o</i> -DCB	$\text{Cu}(\text{OTf})_2$ (10)	150	3	48
8	<i>o</i> -DCB	—	180	24	20
9	<i>o</i> -DCB	$\text{Cu}(\text{OTf})_2$ (2)	180	1	55
10	<i>o</i> -DCB	$\text{Cu}(\text{OTf})_2$ (10)	180	0.5	52

TABLE II. Intramolecular Diels–Alder Reactions of **11a**

Entry	Solvent	Additive (mol %)	Temp., °C	Time, h	Recovery (%) of 11a	Yield (%) of 12a
1	Benzene	$\text{Cu}(\text{OTf})_2$ (10)	Reflux	16	27	58
2	Toluene	—	Reflux	24	88	3
3	Toluene	$\text{Cu}(\text{OTf})_2$ (10)	Reflux	3	0	93
4	<i>o</i> -DCB	—	150	24	73	15
5	<i>o</i> -DCB	$\text{Eu}(\text{fod})_3$ (10)	150	8	47	6
6	<i>o</i> -DCB	$\text{Cu}(\text{OTf})_2$ (2)	150	0.5	0	95

Finally, we focused our attention on the intramolecular Diels–Alder reaction of the unsubstituted substrates (**8b**) and (**11b**). As compared with the dimethyl substituted compounds (**8a**) and (**11a**), the cycloaddition of **8b** and **11b** turned out to be apparently slow and less effective (Table III). Thus, heating a 0.05 M solution of **8b** in *o*-DCB at 180°C for 24 h produced **9b** in a poor yield along with unaltered **8b** (30%) (Entry 1). Even in the presence of $\text{Cu}(\text{OTf})_2$ (10 mol %), the yield of **9b** remained low after 8 h (Entry 3). Although this cycloaddition was somewhat promoted by introduction of the ester group on the terminal olefin of **8b**, the yield of **12b** was moderate (Entry 5).

In conclusion, it has been clarified that the intramolecular Diels–Alder reactions of **8a** and **11a** are considerably accelerated in the presence of $\text{Cu}(\text{OTf})_2$ to provide **9a** and **12a**, respectively, possessing the cyclopenta[*c*]pyridine skeleton, in moderate to excellent yield. The large rate enhancement, namely, the “gem-

dimethyl effect," observed for the dimethyl substituted substrates (**8a**) and (**11a**) may be explained in terms of the "reactive rotamer effect" described by Jung.¹²

TABLE III. Intramolecular Diels–Alder Reactions of **8b** and **11b** in *o*-DCB

Entry	Substrate	Additive (mol %)	Temp., °C	Time, h	Product	Yield, %
1	8b	—	180	24	9b	6
2	8b	Sc(OTf) ₃ (10)	180	8	9b	15
3	8b	Cu(OTf) ₂ (10)	180	8	9b	24
4	11b	Cu(OTf) ₂ (10)	150	4	12b	19
5	11b	Cu(OTf) ₂ (2)	180	2	12b	42
6	11b	Cu(OTf) ₂ (10)	180	1	12b	28

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